REMARKS

Request for Substitution of Sequence Listing based upon Deposit

Applicants request substitution of the sequence listing on file with the sequence listing submitted herewith. Upon re-sequencing the plasmid, 18GC, identified in the instant application (SEQ ID NO:3 and SEQ ID NO:4) on, inter alia, page 4, lines 20-22, of the specification as originally filed and Figures 1A-1C, Applicants have noted three nucleotide discrepancies which did not result in any amino acid change in the amino acid sequence, SEQ ID NO:4, as originally filed. Accordingly, Applicants note that the changes to the substitute sequence listing does not affect the instant claims as amended.

Applicants have deposited the plasmid identified in the application with the ATCC on September 10, 2002. The deposit has been accepted and designated PTA-4654. Applicants, in the instant Response, seek to incorporate the correct sequence into the application with the ATCC deposit, the substitute sequence listing based upon the deposit, amended specification, amended drawings, and declarations. A copy of the papers to accept the sequence of the ATCC deposited organism, filed on December 12, 2002, in a related application, U.S. Application No. 09/886,400, is submitted herewith. Examination of the proper sequences is respectfully requested.

Drawings

Please enter substitute Figure 1, and replace the originally submitted drawing with the formal drawing enclosed herein. The amendment (change in the drawing) is based upon the sequence of *Thermococcus alcaliphilus* AEDII12RA α-galactosidase, 18GC, deposited with the ATCC located at 10801 University Blvd., Manassas, VA 20110-2209, on September 10, 2002, and designated as PTA-4654. Accordingly, Applicants submit that no new matter is introduced by the instant amendment.

Status of the Claims

Pending claims

Claims 1 to 9, 13, 14, and 17 to 45 are pending.

Claims amended, canceled and added in the instant amendment

In the present response, claims 31 to 33, 35 and 38 to 44 are canceled, without prejudice; claims 1 to 3, 5 to 8, 13, 14, 19, 21, 24 to 30, 34, 36, 37 and 42 to 45 are amended; and new claims 46 to 63 are added. Thus, after entry of the instant amendment, claims 1 to 9, 13, 14, 17 to 30, 34, 36, 37, and 42 to 63 are pending and under examination.

Both before and after the above changes and cancellations, and the addition of new claims, the invention was described in full, clear, concise, and exact terms and met all conditions for patentability under 35 USC 101 *et seq*. The scope of the claims of any resulting patent (and any and all limitations in any of said claims) shall not under any circumstances be limited to their literal terms, but are intended to embrace all equivalents.

Outstanding Rejections

Claims 1 to 9, 13, 14, and 17 to 45 are rejected under 35 U.S.C. §112, second paragraph. Claims 24, 25, and 27-45 are rejected under 35 U.S.C. §112, first paragraph. Applicants respectfully traverse all outstanding objections to the specification and rejection of the claims.

Information Disclosure Statement

Applicants submitted a supplementary Information Disclosure Statement (IDS) and Form PTO-1449 on October 10, 2002. It is respectfully requested that the cited information be expressly considered during the prosecution of this application, and the references be made of record and appear among the "references cited" on any patent to issue therefrom.

Support for the Claim Amendments

The specification sets forth an extensive description of the invention in the new and amended claims. Support for claims directed to hybridization wash conditions and stringent hybridization conditions can be found, inter alia, on page 6, lines 2 to 1. Support for claims directed to nucleic acids described by a percent sequence identity to an exemplary nucleic acid can be found, inter alia, on page 6, lines 12 to 21. Support for claims directed to nucleic acids encoding polypeptides with an alpha galactosidase activity comprising hydrolysis of raffinose, stachyose and verbascose can be found, inter alia, on page 2, lines 6 to 8. Support for claims directed to nucleic acids comprising a portion at least 12 contiguous nucleotides of a sequence of

the invention can be found, inter alia, on page 5, last line of the second full paragraph. Support for claims directed to nucleic acids comprising a portion at least 15 contiguous nucleotides of a sequence of the invention can be found, inter alia, on page 9, third full paragraph. Support for claims directed to nucleic acids comprising an antisense strand of a nucleic acid of the invention can be found, inter alia, on page 7, lines 6 to 9. Support for claims directed to cells comprising a nucleic acid of the invention, where the cell is a bacterial cell, a fungal cell, a yeast cell, an insect cell, a plant cell or an animal cell, can be found, inter alia, on the paragraph spanning page 13 to page 14, and on the paragraph spanning page 14 to page 15.

Applicants respectfully request entry of the amendments set forth in this response under 37 CFR §1.116. The amendments place the case in condition for allowance and place the case in better condition for appeal; the amendments do not raise any issues of new matter; and the amended claims do not present new issues requiring further consideration or search.

Objections to the Claims

The Patent Office objects to claims 29 to 45 for the recitation of "isolated fragment." The Patent Office suggests inserting the term "nucleic acid" or "polynucleotide" before the term "fragment." Applicants have amended the claims to obviate this objection.

Issues under 35 U.S.C. §112, second paragraph

The Patent Office rejects claims 1-9, 13, 14, and 17-45 under 35 U.S.C. §112, second paragraph, for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Paragraph 3: the term "complementary"

The Patent Office maintains the rejection of claims 1 (claims 2-4, 6-9, 13, 14, and 17-23 which depend therefrom) and 5 for allegedly being indefinite in the recitation of "a polynucleotide that is complementary."

The Patent Office is concerned that a skilled artisan may not recognize the scope of the complementary polynucleotides encompassed by the claims. The Patent Office alleges that it is unclear whether Applicants' claimed complementary strand is partial complement (i.e., a fragment) or a complete complement.

The instant amendment to the pending claims addresses this issue for claims 1, 2 to 4, 6 to 9, 13, 14 and 17 to 23.

The Patent Office has suggested use of the term "completely complementary" to clarify whether the claimed complementary strand is a partial (*i.e.,* nucleic acid fragment) or a complete complement. Applicants have addressed this issue in new claims 46 and 47.

Paragraphs 4 and 5: the terms "hybridization" and "stringent"

The Patent Office alleges that claims 24 and 32 (claims 40, 41, and 45 which depend therefrom) are indefinite in the recitation of the term "hybridizes" as it is allegedly unclear as to the conditions used for the hybridization. The instant amendment addresses this issue.

The Patent Office alleges that claims 26 and 32 are indefinite in the recitation of the term "stringent conditions" because the specification does not define what conditions constitute "stringent." Applicants respectfully note that conditions that constitute "stringent" are set forth on page 9, the second full paragraph, lines 3 to 7 of the paragraph. The specification notes that "[a]s used herein, the term "stringent conditions" means hybridization will occur only if there is at least 95% and preferably at least 97% identity between sequences." The instant amendment also addresses this issue.

Paragraph 6: the phrase "portion of a polynucleotide"

The Patent Office alleges that claims 29 (claims 35-37 and 42 which depend therefrom), 30, 31 (claims 38, 39, and 44 which depend therefrom), 33, 34 (claims 40, 41, and 45 which depend therefrom) are indefinite for the recitation of "portion of a polynucleotide." One of skill in the art would understand that a "portion" of an article is less than the whole article. Solely to expedite prosecution, Applicants have amended the claims to address this issue.

Paragraph 7: the phrase "the fragment encodes a polynucleotide"

The Patent Office alleges that claim 29 (claims 35-37 and 42 which depend therefrom) is confusing for the recitation of "the fragment encodes a polynucleotide." Applicants have amended claim 29 to obviate this rejection.

Paragraph 8: the phrase "capable of identifying a polynucleotide ... "

The Patent Office alleges that claims 31 (claims 38, 39, and 44 which depend therefrom) and 32-34 (claims 40, 41, and 45 which depend therefrom) are unclear in the recitation of "capable of identifying a polynucleotide encoding a polypeptide having alpha galactosidase activity." Applicants respectfully aver that a skilled artisan would understand what is meant by this phrase. Claims 31 and 32 are directed to polynucleotides with defined physical-chemical structures that enable hybridization to polynucleotides encoding alpha galactosidases. However, in order to expedite prosecution, the instant amendment addresses this issue.

Issues under 35 U.S.C. §112, first paragraph

Applicants note with appreciation the withdrawal of the written description and scope of enablement rejections of claims 1-3, 5-9, and 17-23.

Claims 24, 25, and 27-45 are rejected under 35 U.S.C. §112, first paragraph, for allegedly containing subject matter which was not described in the specification in such as way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Paragraph 10: new matter

The Patent Office alleges that in claim 28 the hybridization condition of "wash in fresh 1X SET at –10 degrees Celsius" is new subject matter. Applicants have amended claim 28 to provide for the wash step found on page 6, lines 4-5, of the specification.

Paragraph 11: written description of the genus of claimed polynucleotides

The Patent Office alleges that the genus of claimed polynucleotides in claims 24, 25, and 27-45 have not been adequately described in the specification. The Patent Office alleges that because the specification describes only a single representative species, the genus of claimed polynucleotides has not been adequately described to satisfy the written description requirements of section 112, first paragraph. It is alleged that the specification fails to describe any other representative specie by any identifying characteristic or properties other that the functionality of hybridizing to a polynucleotide encoding the exemplary polypeptide having alpha galactosidase activity.

Applicants respectfully aver that genus of claimed polynucleotides is sufficiently described in the specification so that one of ordinary skill in the art would be able to ascertain the scope of the claims with reasonable clarity and recognize that Applicants' were in possession of the claimed invention at the time of filing. Applicants respectfully aver that describing a genus of polynucleotides in terms of its physico-chemical properties (e.g., percent sequence identify or stringent hybridization) and function (e.g., alpha galactosidase activity) satisfies the written description requirement of section 112, first paragraph.

Applicants respectfully refer to the USPTO revised interim guidelines concerning compliance with the written description requirement of U.S.C. §112, first paragraph. In example 14 of the guidelines (a copy of which is attached as Appendix A), a claim reciting variants claimed by sequence identity to a sequence is sought (specifically, "A protein having SEQ ID NO:3 and variants thereof that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A → B). In the example, the specification is described as providing SEQ ID NO:3 and a function for the protein. The specification contemplates, but does not exemplify variants of SEQ ID NO:3 that can have substitutions, deletions, insertions and additions (in other words, a genus of polynucleotides). Procedures for making proteins with substitutions, deletions, insertions, and additions are routine in the art and an assay is described which will identify other proteins having the claimed catalytic activity. The analysis of example 14 states that procedures for making variants (which have 95% sequence identity) are conventional in the art. The Guidelines conclusion states that the disclosure meets the requirements of 35 U.S.C. §112, first paragraph, as providing adequate written description for the claimed invention.

Analogously, the claimed nucleic acids are described by structure (the exemplary nucleic acid or polypeptide sequence), a physico-chemical property (e.g., stringent hybridization) and function (alpha galactosidase activity). The specification discloses an exemplary set of hybridization conditions that provides the skilled artisan with the physical/chemical properties of the claimed nucleic acid as well as providing a function for the claimed invention. Accordingly, the specification adequately describes the invention of claim 24 and 28.

The claims fully comply with the requirements for written description of a genus of nucleic acids. In University of California v. Eli Lilly & Co., 43 USPQ2d 1398 (Fed. Cir. 1997), the Federal Circuit stated that, "[a] description of a genus of cDNA may be achieved by

means of a recitation of a representative number of cDNAs....*or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus.*" (emphasis added) Lilly, 43USPQ2d at 1406.

As noted above, the instant claims clearly set forth specific structural and physical characteristics of the claimed alpha galactosidase-encoding nucleic acids. The claimed genus of polypeptides all must have an alpha galactosidase activity and a specific physical characteristic, e.g., stringent hybridization, to the exemplary nucleic acid. Therefore, the claimed sequences are defined via shared physical and structural properties in terms that "convey with reasonable clarity to those skilled in the art that Applicant, as of filing date sought, was in possession of invention." Vas-Cath Inc. V. Mahukar, 19 USPQ2d 1111 (Fed Cir. 1991).

More recently, the Federal Circuit stated

Similarly, in this court's most recent pronouncement, it noted:

> More recently, in Enzo Biochem, we clarified that Eli Lilly did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure.

Amgen, 314 F.3d at 1332 [Amgen Inc. v. Hoechst Marion Roussel Inc., 314 F.3d 1313, 1330, 65 USPQ2d 1385, 1397 (Fed. Cir. 2003)].

Moba, B.V. v. Diamond Automation, Inc., 2003 U.S. App. LEXIS 6285; Fed. Cir. 01-1063, -1083, April 1, 2003.

Analogously, the disclosed function of the alpha galactosidases encoded by the claimed nucleic acids of the instant invention is sufficiently correlated to a particular, known structure (the exemplary sequences) and a physical (physico-chemical) property (stringent hybridization). Accordingly, the claimed sequences are defined via shared physical and structural properties in terms that convey with reasonable clarity to those skilled in the art that Applicants, as of the filing date and at the time of the invention, were in possession of the claimed invention.

Applicants also respectfully note that claims directed to a genus of polypeptides as described and enabled by the specific physical characteristic of stringent hybridization and function have been issuing from the USPTO recently and for many years, see, e.g., U.S. Patent

Nos. 6,541,684; 6,541,236; 6,541,220; 6,534,309; 6,492,150; 6,465,210; 6,413,522; 6,384,304; 6,342,657; 6,274,790 (selected claims from these patents are attached as Appendix B).

Accordingly, Applicants respectfully submit that the pending claims meet the written description requirement under 35 U.S.C. §112, first paragraph.

Paragraph 12: enablement of the genus of claimed polynucleotides

The Patent Office notes that the specification is enabling for the polynucleotide of SEQ ID NO:3. However, it is alleged that the specification does not reasonably provide enablement for the genus of claimed polynucleotides, including polynucleotides that hybridize under any or a specific set of conditions to a polynucleotide encoding SEQ ID NO:4, or a complement thereof, (claim 24) and various permutations of this as described in claims 25 and 27-28), as well as the polynucleotide fragments of claims 29-41.

Applicants respectfully maintain that the specification enabled the skilled artisan at the time of the invention to make and use the genus of claimed polynucleotides as set forth in the claimed invention. The state of the art at the time of the invention and the level of skill of the person of ordinary skill in the art was very high. Hybridization is one of the most basic tools in molecular biology. It is the basis of sequencing, Southern blots, Northern blots, PCR, nucleic acid based screening assays, nucleic acid-based diagnostic assays, to name just a few uses of hybridization.

It would not have taken undue experimentation to make and use the claimed invention. The difference between impermissible undue experimentation and permissible routine experimentation was discussed in the previously submitted response dated August 9, 2002. In brief, in *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, a single deposited antibody producing cell line enabled a claim generic to all IgM antibodies directed to a specific antigen. The Federal Circuit noted that the evidence indicated that those skilled in the monoclonal antibody art could, using the state of the art and applicants' written disclosure, produce and screen new hybridomas secreting other monoclonal antibodies falling within the genus without undue experimentation. The court held that applicants' claims need not be limited to the specific, single antibody secreted by the deposited hybridoma cell line (significantly, the genus of antibodies was allowed even though only one antibody specie was disclosed). The court was acknowledging that, because

practitioners in that art are prepared to screen large numbers of negatives in order to find a sample that has the desired properties, the screening that would be necessary to make additional antibody species was not "undue experimentation."

Analogously, practitioners of the biological sciences for the instant invention also recognize the need to screen large numbers of negatives to find a sample that has the desired properties, e.g., a nucleic acid encoding an alpha galactosidase. Furthermore, the screening procedures used to identify nucleic acids within the scope of the instant invention were all well known in the art and at the time this application was filed and were routine protocols for the skilled artisan. Thus, the skilled artisan using Applicants' written disclosure could practice the claimed invention without undue experimentation.

The instant specification provided SEQ ID NO:3 and SEQ ID NO:4, which one of ordinary skill in the art could use and manipulate to practice the full scope of the claimed invention. For example, the specification provides the skilled artisan with the hybridization conditions and an activity assay to make and use the claimed polynucleotides. Alpha galactosidase activity can be determined by routine experimentation. The specification provides an exemplary method for screening for enzyme activity, see, e.g., Example 2, pages 18 to 19. Accordingly, Applicants respectfully submit that the specification does reasonably provide one of ordinary skill in the art to make and use the subject matter of the claimed invention.

With the guidance provided in the specification, *e.g.*, the structure of the polynucleotides and a functional assay to confirm activity, it would only require the skilled artisan routine experimentation, as is practiced in many laboratories, to practice the full scope of the claimed invention. Accordingly, Applicants respectfully submit that the specification enables one of ordinary skill in the art to practice the full scope of the claimed invention.

Applicants also respectfully note that claims directed to a genus of polypeptides as described and enabled by the specific physical characteristic of stringent hybridization and function have been issuing from the USPTO recently and for many years, see, e.g., U.S. Patent Nos. 6,541,684; 6,541,236; 6,541,220; 6,534,309; 6,492,150; 6,465,210; 6,413,522; 6,384,304; 6,342,657; 6,274,790 (selected claims from these patents are attached as Appendix B).

CONCLUSION

Applicants request that the Examiner reconsider the application and claims in light of the foregoing reasons and amendments and respectfully submit that the claims are in condition for allowance.

If, in the Examiner's opinion, a telephonic interview would expedite the favorable prosecution of the present application, the undersigned attorney would welcome the opportunity to discuss any outstanding issues and to work with the Examiner toward placing the application in condition for allowance.

Applicants believe that no additional fees are necessitated by the present Response. However, in the event any such fees are due, the Commissioner is hereby authorized to charge any such fees to Deposit Account No. 06-1050.

Respectfully submitted,

Date: April 17, 2003

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Figure 1

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TTG AGA GCG CTC GTC TTT CAC GGC AAC CTC CAG TAT GCC GAA ATC CCA      48
Leu Arg Ala Leu Val Phe His Gly Asn Leu Gln Tyr Ala Glu Ile Pro
  5                  10                  15

AAG AGC GAA ATC CCA AAG GTC ATA GAG AAG GCA TAC ATC CCA GTC ATC      96
Lys Ser Glu Ile Pro Lys Val Ile Glu Lys Ala Tyr Ile Pro Val Ile
            20                  25                  30

GAG ACA CTG ATT AAA GAA GAA ATT CCT TTT GGG CTC AAC ATA ACG GGC     144
Glu Thr Leu Ile Lys Glu Glu Ile Pro Phe Gly Leu Asn Ile Thr Gly
        35                  40                  45

TAT ACC TTA AAG TTC CTC CCG AAG GAT ATT ATA GAC CTC GTT AAA GGG     192
Tyr Thr Leu Lys Phe Leu Pro Lys Asp Ile Ile Asp Leu Val Lys Gly
    50                  55                  60

GGC ATC GCG AGT GAC CTG ATA GAG ATA ATC GGA ACG AGC TAC ACG CAC     240
Gly Ile Ala Ser Asp Leu Ile Glu Ile Ile Gly Thr Ser Tyr Thr His
65                  70                  75                  80

GCA ATA CTC CCC CTC CTG CCG CTT AGC AGA GTA GAA GCA CAA GTT CAG     288
Ala Ile Leu Pro Leu Leu Pro Leu Ser Arg Val Glu Ala Gln Val Gln
                85                  90                  95

AGA GAT AGG GAA GTT AAG GAA GAG CTC TTC GAG GTT TCT CCA AAG GGA     336
Arg Asp Arg Glu Val Lys Glu Glu Leu Phe Glu Val Ser Pro Lys Gly
            100                 105                 110

TTC TGG CTG CCA GAG CTC GCC TAT GAC CCG ATA ATC CCT GCC ATA CTG     384
Phe Trp Leu Pro Glu Leu Ala Tyr Asp Pro Ile Ile Pro Ala Ile Leu
        115                 120                 125

AAG GAC AAC GGT TAT GAG TAT CTA TTC GCC GAC GGG GAG GCG ATG CTT     432
Lys Asp Asn Gly Tyr Glu Tyr Leu Phe Ala Asp Gly Glu Ala Met Leu
    130                 135                 140

TTC TCA GCT CAT CTC AAC TCG GCG ATA AAG CCA ATT AAA CCG CTC TAT     480
Phe Ser Ala His Leu Asn Ser Ala Ile Lys Pro Ile Lys Pro Leu Tyr
145                 150                 155                 160

CCA CAC CTT ATA AAG GCC CAA AGG GAA AAG CGC TTT AGG TAC ATC AGC     528
Pro His 3Leu Ile Lys Ala Gln Arg Glu Lys Arg Phe Arg Tyr Ile Ser
                165                 170                 175

TAT CTC CTT GGT CTC AGG GAG CTT AGG AAG GCG ATA AAG CTC GTT TTT     576
Tyr Leu Leu Gly Leu Arg Glu Leu Arg Lys Ala Ile Lys Leu Val Phe
            180                 185                 190

GAA GGT AAG GTA ACG CTA AAG GCA GTC AAA GAC ATC GAA GCC GTA CCC     624
Glu Gly Lys Val Thr Leu Lys Ala Val Lys Asp Ile Glu Ala Val Pro
        195                 200                 205

GTT TGG GTG GCC GTG AAC ACG GCT GTA ATG CTC GGC ATC GGA AGG CTT     672
Val Trp Val Ala Val Asn Thr Ala Val Met Leu Gly Ile Gly Arg Leu
    210                 215                 220

CCT CTT ATG AAT CCT AAG AAA GTG GCG AGC TGG ATA GAG GAC AAG GAC     720
Pro Leu Met Asn Pro Lys Lys Val Ala Ser Trp Ile Glu Asp Lys Asp
225                 230                 235                 240
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AAC ATT CTT CTA TAC GGC ACC GAT ATA GAG TTC ATT GGC TAT AGG GAC     768
Asn Ile Leu Leu Tyr Gly Thr Asp Ile Glu Phe Ile Gly Tyr Arg Asp
                245                 250                 255

ATT GCA GGC TAC AGA ATG AGT GTT GAG GGA TTA TTA GAG GTT ATA GAC     816
Ile Ala Gly Tyr Arg Met Ser Val Glu Gly Leu Leu Glu Val Ile Asp
            260                 265                 270

GAG CTC AAC TCG GAA CTG TGC CTT CCC TCA GAG CTG AAG CAC AGT GGA     864
Glu Leu Asn Ser Glu Leu Cys Leu Pro Ser Glu Leu Lys His Ser Gly
        275                 280                 285

AGG GAG CTC TAC TTA CGG ACT TCG AGT TGG GCA CCA GAT AAG AGC TTG     912
Arg Glu Leu Tyr Leu Arg Thr Ser Ser Trp Ala Pro Asp Lys Ser Leu
    290                 295                 300

AGG ATA TGG AGA GAG GAC GAA GGG AAC GCA AGA CTT AAT ATG CTG TCC     960
Arg Ile Trp Arg Glu Asp Glu Gly Asn Ala Arg Leu Asn Met Leu Ser
305                 310                 315                 320

TAC AAT ATG AGG GGC GAA CTC GCC TTT TTA GCC GAG AAC AGC GAT GCA    1008
Tyr Asn Met Arg Gly Glu Leu Ala Phe Leu Ala Glu Asn Ser Asp Ala
                325                 330                 335

AGG GGA TGG GAG CCC CTC CCT GAG AGG AGG CTG GAT GCC TTC CGG GCG    1047
Arg Gly Trp Glu Pro Leu Pro Glu Arg Arg Leu Asp Ala Phe Arg Ala
            340                 345                 350

ATA TAT AAC GAT TGG AGG GGT GAA AAT GGG GAA CCT TAG                1086
Ile Tyr Asn Asp Trp Arg Gly Glu Asn Gly Glu Pro End
        355                 360                 365
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